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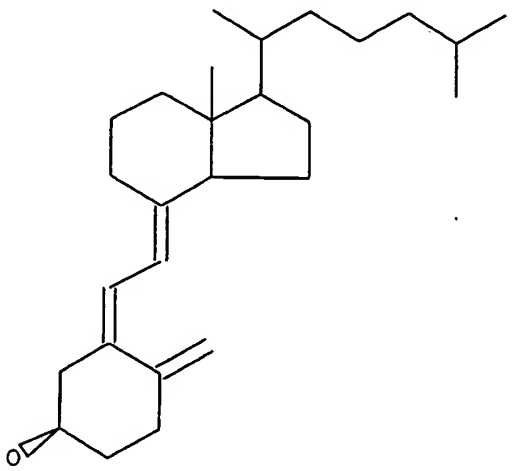
(54) Title: USES OF 1,25-DIHYDROXY-5,6-*trans* VITAMIN D COMPOUNDS AND DERIVATIVES THEREOF

(57) Abstract: 1,25-dihydroxy-5,6-*trans* vitamin D compounds and their derivatives, especially the esters, are useful in the treatment or prevention of diseases characterised by abnormall cell differentiation or cell proliferation, as well as other diseases or conditions treatable with vitamin D compounds, such as osteoporosis and other metabolic bone diseases, and are not associated with the degree of hypercalcaemia observed wtih 1,25-dihydroxy vitamin D_3.

USES OF 1,25-DIHYDROXY-5,6-*trans* VITAMIN D COMPOUNDS AND DERIVATIVES THEREOF

The present invention relates to the use of vitamin D analogues and their derivatives in medicine, particularly in the treatment or prevention of diseases characterised by abnormal cell differentiation or cell proliferation, as well as other diseases or conditions treatable with vitamin D compounds, including renal osteodystrophy, hypoparathyroidism, and metabolic bone diseases such as osteoporosis.

Vitamin D_3 has the structure:



It is well known that vitamin D_3 plays a vital role in the metabolism of calcium, by promoting intestinal absorption of calcium and phosphorus, maintaining adequate serum levels of calcium and phosphorus, and stimulating mobilisation of calcium from the bone fluid compartment in the presence of parathyroid hormone [Holick, M. F., in "Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism", M. J. Favus (ed.), 4th Ed., Lippincott-Williams & Wilkins: Philadelphia (1999), pp. 92-98].

To become biologically active, vitamin D_3 must undergo two hydroxylation steps. The first hydroxylation step occurs in the liver, by hydroxylation at C-25, thereby forming 25-hydroxyvitamin D_3 [25-(OH)D_3], the major circulating metabolite of vitamin D_3. The second hydroxylation occurs in the kidney, by hydroxylation at the 1α -position, forming 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2$-D_3], which is the hormonally active metabolite.

1,25-$(OH)_2$-D_3 is the most active form of vitamin D, and is intimately involved in calcium and phosphorous homeostasis, both in animals and humans. Its principal physiological function is on calcium and bone metabolism, stimulating intestinal calcium transport and initiating mobilisation of calcium stores from bone, as noted above. Patients with kidney failure, so who are unable to make 1,25-$(OH)_2$-D_3, develop hypocalcaemia, secondary hyperparathyroidism, and the bone disease renal osteodystrophy. Accordingly, administration of 1,25-$(OH)_2$-D_3 is useful in the treatment of disorders of calcium and bone metabolism, such as renal osteodystrophy, vitamin D-dependent rickets, low blood serum calcium due to hypoparathyroidism, and particularly osteoporosis, as it compensates for the lack of the naturally occurring metabolite, and stimulates calcium uptake in the gut.

1,25-$(OH)_2$-D_3 is able to carry out most of its biological effects by interacting with a specific receptor known as the vitamin D receptor (VDR). VDR is present in tissues that are responsible for regulating calcium and bone metabolism, including the small intestine, kidney and bone. In addition, a wide variety of tissues and cells, not related to calcium and bone metabolism, also possess VDR (Holick, M. F., "Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism", *supra*). These include, among others, brain, heart, gonads, breast, pancreas, skeletal muscle, smooth muscle, skin, monocytes, and activated T and B lymphocytes. In addition, several tumour cell lines, including promyelocytic leukaemic cells, multiple myeloma cells, squamous cell carcinoma cells, prostate cancer cells, breast cancer cells, and basal cell carcinoma cells, possess VDR [Holick, M. F., Bone, **17**, (Suppl.):107S-111S (1995)].

Although the exact function of VDR in such tissues and cells is not well understood, it is known that some cells possessing VDR decrease their proliferative activity in respose to 1,25-$(OH)_2$-D_3. Multiple studies have shown that several lines of cancer cells possessing a VDR, including colon, melanoma, prostate and breast, when incubated with 1,25-$(OH)_2$-D_3, decreased their proliferation [Holick, M. F., Bone, *supra*; Halline, A. G., *et al.*, Endocrinology **134**:1710-1717 (1994); Konety, B. R., *et al.*, Cell Growth & Differentiation 7:1563-1570 (1996); and Kivineva, M., *et al.*, J. Steroid Biochem. Mol. Biol. **66**:121-127 (1998)]. In addition, some cells, such as keratinocytes, are also induced into terminal differentiatiation.

Thus, 1,25-$(OH)_2$-D_3 has been shown to stimulate the differentiation of cells and to inhibit excessive cell proliferation [*c.f.* Walter, M. R., Endocr. Rev. **13**:719-764 (1992); see also Schwartz, G. G., Anticancer Res. 14:1077-1082 (1994); Amento *et al.*, J. Clin. Invest. **73**:731-739 (1984); Tanaka *et al.*, Biochem. J. **204**:713-719 (1982); Abe, E., *et al.*, Proc. Natl. Acad. Sci., U.S.A. **78**:4990-4994 (1981); and Colston *et al.*, Endocrinology **108**:1083-1086 (1981)]. This effect has given rise to the use of 1,25-$(OH)_2$-D_3 and its analogues for treating hyperproliferative skin diseases such as psoriasis, and has suggested the possibility for treating some cancers such as breast, colon, and prostate [Holick, M. F., Bone *supra*; Gross, C., *et al.*, in Vitamin D, D. Feldman *et al.* (eds.), Academic Press: New York (1997), pp. 1125-1139; U.S. Patent Nos. 4,728,643 and 5,037,816].

In addition to regulating calcium and phosphorus homeostasis and stimulating cell growth and differentiation, 1,25-$(OH)_2$-D_3 has also been shown to have various additional effects on cellular metabolism.

For example, a potential therapeutic use for 1,25-$(OH)_2$-D_3 is suggested by the observation of an association between hereditary vitamin D resistance and alopecia: treatment with 1,25-$(OH)_2$-D_3 may promote hair growth [Editorial, Lancet, Mar. 4, (1989), p. 478]. Moreover, the fact that topical application of 1,25-$(OH)_2$-D_3 reduces the size of sebaceous glands in the ears of male Syrian hamsters suggests that this

compound might be useful for the treatment of acne [Malloy, V. L., *et al.*, The Tricontinental Meeting for Investigative Dermatology, Washington, (1989)]. Use of 1,25-$(OH)_2$-D_3, or its pro-drug, 1-(OH)D_3, for the treatment of hypertension [Lind, L., *et al.*, Acta Med. Scand. **222**:423-427 (1987)] and diabetes mellitus [Inomata, S., *et al.*, Bone Mineral. **1**:187-192 (1986)], has also been suggested.

The potential therapeutic applications suggested above, however, are severely limited by the risk of hypercalcaemia, a condition resulting from elevated blood serum concentrations of 1,25-$(OH)_2$-D_3 which often occurs during exogenous administration of the compound (Holick, M. F., "Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism", *supra*). Hypercalcaemia is a potentially fatal condition, if not controlled, making administration of large amounts of 1,25-$(OH)_2$-D_3 undesirable. Further, even topical administration has been demonstrated to lead to elevated levels of serum calcium, so that administration of 1,25-$(OH)_2$-D_3 is, therefore, not even completely satisfactory for use as a drug in the treatment of, for example, psoriasis or leukaemia, which may require continuous administration of the drug in relatively high doses.

Accordingly, a number of structural analogues of 1,25-$(OH)_2$-D_3 and its precursors have been prepared, including fluorinated analogues [*c.f.* DeLuca and Schnoes, Ann. Rev. Biochem. **52**:411-439 (1983)] and compounds containing the vitamin D nucleus, but with altered or additional side chains (*c.f.* U.S. Patent Nos. 5,945,410; 5,932,565; 5,843,928; and 5,554,599).

The *trans* forms of both vitamin D_3 and 25-hydroxyvitamin D_3 [5,6-*trans* D_3 and 5,6-*trans*-25-(OH)D_3] have also been prepared as vitamin D_3 structural analogues [Holick *et al.*, Biochemistry **11**:2715 (1972); Holick *et al.*, Science **176**:1247 (1972)]. These latter two compounds possess biological activity similar to that of naturally occurring 1,25-$(OH)_2$-D_3, in that each stimulates a biological response in anephric animals similar to that elicited by 1,25-$(OH)_2$-D_3. 5,6-*trans* D_3 stimulates intestinal calcium transport as well as bone calcium mobilisation from bone in anephric rats,

while 5,6-*trans*-25-(OH)D_3 only stimulates intestinal calcium transport [Holick *et al.*, Biochemistry **11**:2715 (1972); Holick *et al.*, Science **176**:1247 (1972)]. The naturally occurring *cis* analogues, D_3 and 25-(OH)D_3, are inactive in anephric rats.

A need continues to exist for new methods for the treatment of disorders involving calcium and phosphorus metabolism, such as osteoporosis, and the treatment or prevention of diseases characterised by abnormal cell differentiation or cell proliferation, as well as other diseases or conditions treatable with vitamin D compounds.

Surprisingly, the *trans* forms of the 1,25-dihydroxyvitamin D compounds, while retaining many, if not all, of the therapeutic advantages of the naturally occurring *cis* compounds, are significantly less active in the gut, thereby allowing use of greater amounts of the *trans* form, without the risk of hypercalcaemia associated with the naturally occurring *cis* compounds.

Thus, in a first aspect, the present invention provides a 1,25-dihydroxy-5,6-*trans* vitamin D compound, or a pharmaceutically acceptable derivative thereof, for use in therapy.

The present invention extends to any vitamin D compound, but applies, more preferably to vitamins D_2 and D_3. Of these, vitamin D_3 is particularly preferred, with vitamin D_2 generally being used as a vitamin D_3 substitute. Thus, the preferred compound for use in the present invention is 1,25-dihydroxy-5,6-*trans* vitamin D_3. Where vitamin D_3 and its hydroxy, and *trans* analogues, is mentioned herein, then it will be understood that reference is also had to other vitamin D compounds, unless otherwise indicated or apparent.

By pharmaceutically acceptable derivative is meant anything that can be administered to a patient without unacceptable levels of toxicity. In particular, there are provided the esters and orthoesters of vitamin D, especially vitamin D_3. Another

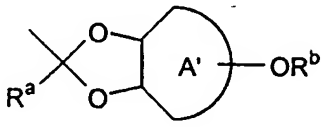
preferred group of derivatives is the glycosides and their amino derivatives.

When the derivative of the present invention is a glycoside or orthoester glycoside derivative, then it may be straight or branched chain, and may be a mono- or di- glycoside, that is, it occurs on either the 1- or 25- positions, or both. In addition, the derivative may be mixed with, for example, a glycoside in the 1- position and a citrate in the 25- position, although there will generally be no requirement for such a compound which, in any case, is generally more difficult to prepare. Thus, as with other derivatives, the diglycoside is generally preferred, for ease of manufacture.

It will also be appreciated that the glycosides, as with other hydroxyester side chains, may be further esterified, preferably by lower alkanoyl groups, especially acetyl groups.

Preferred glycosides contain 1-20 glycosidic units. More preferably, the glycoside is a mono-, di- or tri- saccharide, and is preferably a glycopyranosyl group, particularly a 1′–β-glucopyranosyl group.

When the derivative is an orthoester glycoside, then it preferably has the Formula (II):



(II)

wherein A' represents a glycofuranosyl or glycopyranosyl ring;

R_a is H, C_{1-4} alkyl, C_{7-10} aralkyl, phenyl or phenyl substituted by chloro, fluoro, bromo, iodo, C_{1-4} alkyl or C_{1-4} alkoxy, or is naphthyl; and

R_b is H or a straight or branched chain glycosidic residue containing 1-20 glycosidic units.

In general, the derivatives of the present invention serve as protected precursors of the parent vitamin D compound, and the protecting group is metabolically cleaved to yield the active compound.

Essentially, 1,25-dihydroxy-5,6-*trans* vitamin D_3 and its esters can be used, instead of 1,25-dihydroxyvitamin D_3, wherever the latter would otherwise be indicated, save where increased calcium uptake from the gut is specifically required. The compounds of the invention also have the advantage that they do not stimulate loss of calcium from bones and, may be used, if deemed appropriate by a skilled clinician, together with 1,25-$(OH)_2$vitamin D_3, if desired.

In general, it is preferred to use the unesterified 1,25-dihydroxy-5,6-*trans* vitamin D_3, whether for oral or topical administration. Although other administration forms are not ruled out, the most convenient routes of administration for any form of vitamin D are oral and topical.

Any pharmaceutically acceptable ester may be employed, provided that, *in situ*, 1,25-dihydroxy-5,6-*trans* vitamin D_3 will be available. Thus, for topical administration, as there will be little or no metabolic processing prior to reaching the target cells, the preferred form is the parent compound.

However, for oral administration, in order to reduce the effect on mucosal uptake of calcium, it may be preferred to employ an ester. Suitable esters include, for example, the acetate, citrate and glucuronic esters.

The present invention further provides a medicament, or pharmaceutical composition, comprising 1,25-dihydroxy-5,6-*trans* vitamin D_3, or a pharmaceutically acceptable ester thereof, and a pharmaceutically acceptable carrier therefor.

The invention further provides a method for the treatment or prophylaxis of a condition, other than hypocalcaemia, responsive to treatment with a vitamin D

compound, especially 1,25-dihydroxyvitamin D_3, comprising administering 1,25-dihydroxy-5,6-*trans* vitamin D_3, or a pharmaceutically acceptable ester thereof, to an animal in need thereof. The animal is preferably mammalian and, more preferably, human.

In the alternative, there is provided a method for the treatment or prophylaxis of a disease or condition characterised by abnormal cell differentiation or cell proliferation in an animal, comprising administering to the cells of the animal in need thereof an effective amount of 1,25-dihydroxy-5,6-*trans* vitamin D_3, or a pharmaceutically acceptable ester thereof, whereby the disease or condition is treated or prevented.

It will be appreciated that there is also provided use of 1,25-dihydroxy-5,6-*trans* vitamin D_3, or a pharmaceutically acceptable ester thereof, in the manufacture of a medicament for the treatment or prophylaxis of a disease or condition as described herein, particularly those treatable by 1,25-dihydroxy vitamin D_3, other than hypocalcaemia.

The present invention also extends to the novel derivatives, especially the esters, of 1,25-dihydroxy-5,6-*trans* vitamin D_3 and D_2, especially the acetate, citrate and glucuronic esters of vitamin D_3, the acetate being most preferred. The esters may be single or double esters, the double esters generally being preferred.

A suitable category of condition for treatment with compounds of the present invention include metabolic bone diseases (including osteoporosis, for example), renal osteodystrophy, and hypoparathyroidism.

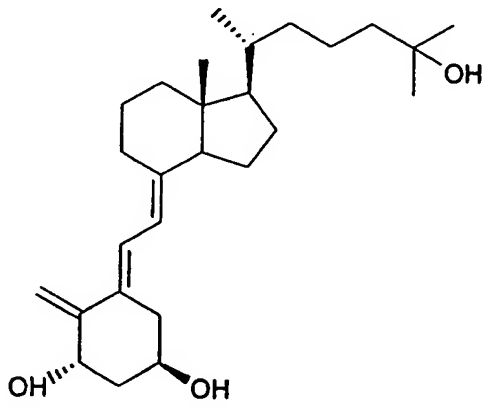
Another suitable category is those diseases and conditions characterised by abnormal cell differentiation or cell proliferation. In particular, hyperproliferative skin disorders may be targetted, and these include psoriasis, ichthyosis, and actinic keratoses.

Another preferred disease category for treatment or prophylaxis, including after care, is cancer. Compounds of the invention may be used to inhibit the proliferation of tumour cells, or used to induce differentiation of tumour cells. Suitable targets include prostate cancer, breast cancer, skin cancer, colon cancer, leukaemias, lymphomas, and lung cancer.

Disorders in calcium and bone metabolism may also be treated. Suitable disorders for treatment include; vitamin D-dependent rickets type I, X-linked hypophosphataemic rickets, vitamin D-dependent rickets type II, renal osteodystrophy, low blood serum calcium due to hypoparathyroidism, and, in particular, osteoporosis.

Figure 1 shows the effect of 5,6-*trans*-1,25-$(OH)_2$-D_3 in comparison to 1,25-$(OH)_2$-D_3 on inhibition of proliferation of cultured human keratinocytes.

1,25-dihydroxy-5,6-*trans* vitamin D_3 [5,6-*trans*-1,25-$(OH)_2$-D_3] has the Formula (I):



(I)

Hyperproliferative skin disorders include such disorders as psoriasis, ichthyosis, and actinic keratoses, a pre-skin cancer, and even such conditions as benign prostatic hyperplasia. Administration of 5,6-*trans*-1,25-$(OH)_2$-D_3 results in a

decrease in proliferative activity and induces the affected cells to differentiate into normal morphology.

Preferred cancers to be targetted by the present invention are those whose cells express the vitamin D receptor (VDR), including prostate cancer, breast cancer, skin cancer, colon cancer, leukemias, lymphomas, and lung cancer.

Disorders in calcium and bone metabolism include such conditions as renal osteodystrophy, vitamin D-dependent rickets type I, X-linked hypophosphataemic rickets, vitamin D-dependent rickets type II, and osteoporosis, as well as such disorders in calcium and bone metabolism as low blood serum calcium due to hypoparathyroidism. It is particularly preferred to treat osteoporosis.

5,6-*trans*-1,25-$(OH)_2$-D_3 can be synthesised following any known method of synthesis of the compound, such as that described in Andrews, D. R., *et al.*, J. Org. Chem. **51**(25):4819-4828 (1986), which relates to the synthesis of 1,25-$(OH)_2$-D_3.

The compounds of the present invention are intended for use in pharmaceutical compositions which are useful in the treatment of human and veterinary disorders as described above.

5,6-*trans*-1,25-$(OH)_2$-D_3 can be administered in any appropriate pharmaceutically acceptable carrier for oral, parenteral, or topical administration. It can be administered by any suitable means for the treatment or prevention of conditions or diseases as exemplified herein, including diseases characterised by abnormal cell differentiation or cell proliferation, or other conditions treatable with vitamin D compounds (metabolic bone diseases such as osteoporosis, or inflammation, for example), in animals, especially humans.

Suitable mammals for treatment include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits, mice and humans. Particularly preferred are humans.

Dosage forms of the various compounds can be prepared by combining them with non-toxic pharmaceutically acceptable carriers to make either immediate release or slow release formulations, as is well known in the art. Such carriers may be either solid or liquid such as, for example, corn starch, lactose, sucrose, peanut oil, olive oil, sesame oil and propylene glycol. If a solid carrier is used the dosage form of the compounds may be tablets, capsules, powders, troches or lozenges. If a liquid carrier is used, soft gelatin capsules, or syrup or liquid suspensions, emulsions or solutions may be the dosage form. The dosage forms may also contain adjuvants, such as preserving, stabilising, wetting or emulsifying agents, solution promoters, *etc.* They may also contain other therapeutically active agents.

The dosage administered will be an amount effective to achieve the intended purpose and will be dependent upon the age, health and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. For example, systemic daily dosage of 5,6-*trans*-1,25-$(OH)_2$-D_3 will be from about 0.001 micrograms/kg to 100 micrograms/kg, preferably 0.01 to 10.0 micrograms per kg of body weight. Normally, from about 0.1 to 100 micrograms/kg per day of 5,6-*trans*-1,25-$(OH)_2$-D_3, in one or more dosages per day, is effective to obtain the desired results. Suitable topical dosages are from 0.001 micrograms to 100 micrograms/cm^2 area of skin. One of ordinary skill in the art can determine the optimal dosage and concentration with only routine experimentation.

5,6-*trans*-1,25-$(OH)_2$-D_3 can be employed in dosage forms such as tablets, capsules, powder packets, or liquid solutions, suspensions or elixirs for oral administration, sterile liquid for formulations, such as solutions or suspensions for parenteral use. Alternatively, the compound may be administered transdermally *via* a patch or ointment and the like. 5,6-*trans*-1,25-$(OH)_2$-D_3, as the active ingredient, will ordinarily be present in an amount of at least 10^{-6} % by weight based upon the total weight of the composition, and not more than 90% by weight. An inert pharmaceutically acceptable carrier is preferably used. Among such carriers include 95% ethanol, vegetable oils, propylene glycols, saline buffers, *etc.*

Formulations suitable for topical administration include liquid or semi-liquid preparations such as liniments, lotions, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops; or as sprays.

The topical compositions of this invention are formulated preferably as creams, lotions, ointments and the like by choice of appropriate carriers. Suitable carriers include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohol (greater than C_{12}). The preferred carriers are those in which the active ingredient is soluble. Emulsifiers, stabilisers and antioxidants may also be included as well as agents imparting colour or fragrance if desired.

Topical creams are preferably formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture the active ingredient, dissolved in a small amount of an oil such as almond oil, is admixed. A typical example of such a cream is one which includes about 39 parts water, about 20 parts beeswax, about 40 parts mineral oil and about 1 part almond oil.

Topical ointments may be formulated by mixing a solution of the active ingredient in a vegetable oil such as almond oil with warm soft paraffin and allowing the mixture to cool. A typical example of such an ointment is one which includes about 30% almond oil and about 70% white soft paraffin by weight.

Topical lotions may be conveniently prepared by dissolving the active ingredient, in a suitable high molecular weight alcohol such as propylene glycol or polyethylene glycol.

The following Examples are illustrative, but not limiting, of the methods of the present invention.

EXAMPLE 1

PREPARATION OF 1,25-DIHYDROXY-5,6-*TRANS* VITAMIN D_3

5,6-*trans*-1,25-$(OH)_2$-D_3 can be synthesised following any known method of synthesis of the compound, such as that described in Andrews, D. R., *et al.*, J. Org. Chem. 51(25):4819-4828 (1986). Following this technique, crystals of the title compound, were analysed using standard protocols, and had the following properties:

Melting point: 172-173°C;
Optical rotation: $[\alpha]_D$ +189.09 © 0.165, EtOH);
Absorption spectrum: UV (EtOH): 208 nm (E13,380), 273 (24,100);
Analysis: Calculated: C 77.84, H 10.65. Found: C 77.63, H 10.61;
^{1}NMR (CD_3OD): δ 0.60 (s, CH_3, 3H), 0.98 (d, CH-CH_3, 3H), 1.19 (s, CH_3, 3H), 2.60-3.00 (m, =CH + CH_2, 3H), 4.09 (m, CH-OH, 1H), 4.40 (m, CH-OH, 1H), 4.95 and 5.05 (d, =CH_2, 2H), 5.89 (d, =CH, 1H), 6.52 (d, =CH, 1H).

EXAMPLE 2

EFFECT OF 5,6-*TRANS*-1,25-$(OH)_2$-D_3 ON INHIBITION OF PROLIFERATION OF CULTURED HUMAN KERATINOCYTES

The effect of 5,6-*trans*-1,25-$(OH)_2$-D_3 on inhibition of the proliferation of cultured human keratinocytes was tested and compared to that of 1,25-$(OH)_2$-D_3.

Second passage normal human keratinocytes were treated with 0, 10^{-9}, 10^{-8}, and 10^{-7} M of 1,25-$(OH)_2$-D_3 or 5,6-*trans*-1,25-$(OH)_2$-D_3 in the presence of basal MCDB media plus 25 ng/ml EGF at 37°C, following experimental methods previously described [Smith, E. L., Walworth, N., Holick, M.F., "Effect of 1,25-

dihydroxy vitamin D_3 on the morphologic and biochemical differentiation of cultured human epithelial keratinocytes grown in serum-free conditions," J. Invest. Dermatol. 86:709-714 (1986)]. Eighteen hours later, [^{3}H]-thymidine incorporation into DNA was performed.

The results, expressed as percent of control, are shown in Figure 1 [Key - Cultured human keratinocytes were incubated with 5,6-*trans*-1,25-$(OH)_2$-D_3 or 1,25-$(OH)_2$-D_3 at different concentrations (1nM,10nM, 100nM) for eighteen hours. [^{3}H]thymidine incorporation was measured as described. •-•: [^{3}H]thymidine incorporation of cells incubated with 1,25-$(OH)_2$-D_3; □-□: [^{3}H]thymidine incorporation of cells incubated with 5,6-*trans*-1,25-$(OH)_2$-D_3. Results are expressed as percent of control values].

As Figure 1 indicates, 5,6-*trans*-1,25-$(OH)_2$-D_3 inhibits the growth of normal human keratinocytes, and it does so to roughly the same degree as its naturally-occurring *cis* analogue, 1,25-$(OH)_2$-D_3.

Having now fully described the invention, it will be understood to those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof. All patents and publications cited herein are fully incorporated by reference herein in the entirety.

Claims:

1. A 1,25-dihydroxy-5,6-*trans* vitamin D compound, or a pharmaceutically acceptable derivative thereof, for use in therapy.

2. A compound for use according to claim 1, which is 1,25-dihydroxy-5,6-*trans* vitamin D_3, or a pharmaceutically acceptable derivative thereof, for use in therapy.

3. A compound for use according to claim 1, which is 1,25-dihydroxy-5,6-*trans* vitamin D_2, or a pharmaceutically acceptable derivative thereof, for use in therapy.

4. A compound for use according to any preceding claim, which is a glycoside or orthoester glycoside derivative of said vitamin D compound.

5. A compound as defined in of claims 1 to 3, in the form of the acetic, citric or glucuronic ester thereof.

6. A compound according to any preceding claim, for use in an indication in which 1,25-dihydroxyvitamin D_3 would otherwise be indicated.

7. A compound according to any preceding claim, for use in the treatment or prophylaxis of a disease or condition characterised by abnormal cell differentiation or cell proliferation.

8. A compound for use according to claim 7, wherein the disease or condition is a hyperproliferative skin disorder.

9. A compound for use according to claim 8, wherein the hyperproliferative skin disorder is selected from psoriasis, ichthyosis, and actinic keratoses.

10. A compound for use according to claim 7, wherein the disease or condition is

prostate cancer, breast cancer, skin cancer, colon cancer, lung cancer, leukaemia, or lymphoma.

11. A compound for use according to claim 7, wherein the disease or condition is a disorder in calcium and bone metabolism.

12. A compound for use according to claim 11, wherein the disorder in calcium and bone metabolism is vitamin D-dependent rickets type I, X-linked hypophosphataemic rickets, vitamin D-dependent rickets type II, or osteoporosis.

13. A compound for use according to claim 11, wherein the disorder is renal osteodystrophy.

14. A compound for use according to claim 11, wherein the disorder is low blood serum calcium due to hypoparathyroidism.

15. A compound for use according to claim 11, wherein the disorder is osteoporosis.

16. A compound according to any preceding claim, in a formulation suitable for oral administration.

17. A compound according to any of claims 1 to 15, in a formulation suitable for topical administration.

18. A compound according to any of claims 1 to 15, in a formulation suitable for systemic administration.

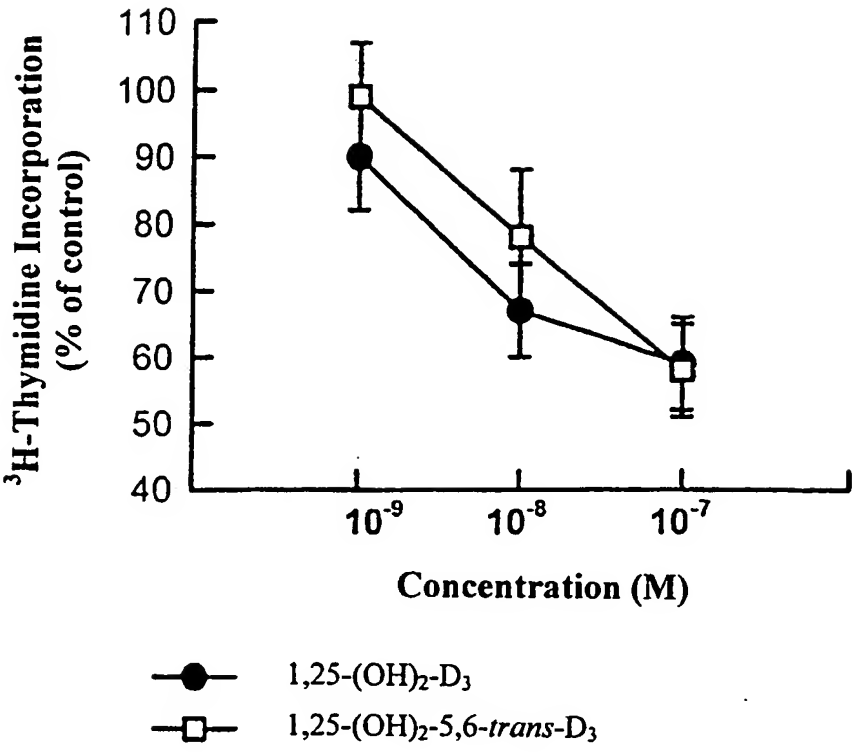

^{3}H-Thymidine Incorporation (% of control)
110
100
90
80
70
60
50
40
10^{-9}
10^{-8}
10^{-7}
Concentration (M)
1,25-$(OH)_2$-D_3
1,25-$(OH)_2$-5,6-*trans*-D_3

Fig. 1

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(71) Applicant *(for all designated States except US)*: **STRAKAN LIMITED** [—/—]; 22 Church Street, Hamilton HM11 (BM).

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(74) Agent: **LORD, Hilton, David**; Marks & Clerk, 57-60 Lincoln's Inn Fields, London WC2A 3LS (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: USES OF 1,25-DIHYDROXY-5,6-*trans* VITAMIN D COMPOUNDS AND DERIVATIVES THEREOF

(57) Abstract: 1,25-dihydroxy-5,6-*trans* vitamin D compounds and their derivatives, especially the esters, are useful in the treatment or prevention of diseases characterised by abnormall cell differentiation or cell proliferation, as well as other diseases or conditions treatable with vitamin D compounds, such as osteoporosis and other metabolic bone diseases, and are not associated with the degree of hypercalcaemia observed wtih 1,25-dihydroxy vitamin D_3.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/04120

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/593 C07C401/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kyriakakou, G

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